IN THE SUPREME COURT OF THE UNITED STATES

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MERCK KGaA, :

Petitioner, :

v. : No. 03-1237

INTEGRA LIFESCIENCES I, :

LTD., ET AL. :

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Washington, D.C.

Wednesday, April 20, 2005

The above-entitled matter came on for oral argument before the Supreme Court of the United States at 10:03 a.m.

APPEARANCES:

E. JOSHUA ROSENKRANZ, ESQ., New York, New York; on behalf of the Petitioner.

MR. DARYL JOSEFFER, ESQ., Assistant to the Solicitor General, Department of Justice, Washington, D.C.; for United States, as amicus curiae, supporting the Petitioner.

MAURICIO A. FLORES, ESQ., Irvine, California; on behalf of the Respondents.

C O N T E N T S

P R O C E E D I In G S

[10:03 a.m.]

CHIEF JUSTICE REHNQUIST: We'll hear argument now in the Merck KGaA v. Integra Lifesciences.

Mr. Rosenkranz.

ORAL ARGUMENT OF E. JOSHUA ROSENKRANZ

ON BEHALF OF PETITIONER

MR. ROSENKRANZ: Thank you, Your -- Mr. Chief Justice, and may it please the Court:

Your Honors, there is no dispute among the parties, nor among the 19 amicus briefs presented before the Court today. As to the answer to the threshold legal question, everyone agrees that the FDA exemption does, indeed, apply, with full course, to the sorts of experiments that are conducted and that would be relevant to the FDA in consideration of an Investigational New Drug application, a so-called IND. So the battleground now shifts to Integra's alternative arguments in support of the judgement --

JUSTICE O'CONNOR: Well, would you just clarify something for me as we start to consider the case? I guess this thing went to the jury under an instruction that tried to come to grips with the definition under the statute in some way. Was that instruction one to which Merck preserved an objection?

MR. ROSENKRANZ: No, Your Honor. We did not object to the core of the jury's instructions stating the legal standard. And we --

JUSTICE O'CONNOR: Do you think it was properly stated in that instruction?

MR. ROSENKRANZ: The core of the instruction, yes, Your Honor, was --

JUSTICE O'CONNOR: That's as good as we could do.

MR. ROSENKRANZ: Your Honor, I believe -- the answer is, the core was as good as this Court can do, and

JUSTICE O'CONNOR: All right. And, under that, you think that Merck was entitled to a directed verdict --

MR. ROSENKRANZ: Yes, Your Honor.

JUSTICE O'CONNOR: -- from the evidence?

MR. ROSENKRANZ: It was entitled to a verdict as a matter of law, but let me just --

JUSTICE O'CONNOR: Okay, but the Court of Appeals for the Federal Circuit did not address the case in -- by looking at the evidence and whether a directed verdict should have been given --

MR. ROSENKRANZ: Your Honor, the --

JUSTICE O'CONNOR: -- or not?

MR. ROSENKRANZ: -- the Federal Circuit did

understand that this was a JMOL case --

JUSTICE O'CONNOR: No, but it seemed to decide the case based on its view of the statute as just applying to generic drugs or something --

MR. ROSENKRANZ: That is absolutely correct, Your Honor.

JUSTICE O'CONNOR: So it didn't, in fact, come to grips with the evidence.

MR. ROSENKRANZ: It absolutely did not come to grips with the evidence, nor did it grapple with the alternative arguments that Integra was presenting --

JUSTICE O'CONNOR: Yeah, so --

MR. ROSENKRANZ: -- so they --

JUSTICE O'CONNOR: -- maybe all we have to do is deal with whether that court should have addressed the evidence.

MR. ROSENKRANZ: That would be one answer, Your Honor, reverse and not addressing the alternative legal grounds, but I would urge this Court to address the alternative grounds, because they raise --

JUSTICE O'CONNOR: All of them? You mean, like the research tools problem?

MR. ROSENKRANZ: No, Your Honor, because the research tools problem was never presented --

JUSTICE O'CONNOR: No.

MR. ROSENKRANZ: -- as an issue before the jury or before the District Court. And --

JUSTICE O'CONNOR: Or the Tripps Treaty?

MR. ROSENKRANZ: No, Your Honor.

JUSTICE O'CONNOR: No.

MR. ROSENKRANZ: In fact, that's not even raised by Respondents. It's raised by --

JUSTICE O'CONNOR: All right. And how about the common-law research --

MR. ROSENKRANZ: I would -- I would urge the Court not broach the subject of any of the questions that are not properly presented --

JUSTICE O'CONNOR: Okay, so --

MR. ROSENKRANZ: -- to this Court.

JUSTICE O'CONNOR: -- all we're doing is looking at the statute.

MR. ROSENKRANZ: We're --

JUSTICE O'CONNOR: Thank you.

MR. ROSENKRANZ: Yes, Your Honor, we're looking at the statute --

JUSTICE O'CONNOR: Okay.

MR. ROSENKRANZ: -- but it is an -- it is important, in answer to the very first question, to embellish a bit, because the lower courts need this Court's guidance, because every one of the theories on

which Integra defends the judgement below raise exactly the same problems that the Federal Circuit's opinion raises. They defy the plain language of the statute Congress passed. They are equally at odds with the purpose that Congress had in mind when it passed the FDA exemption.

CHIEF JUSTICE REHNQUIST: What are the alternative grounds that you're discussing now passed on by the Federal Circuit?

MR. ROSENKRANZ: Your Honor, they were not passed on by the Federal Circuit, except perhaps to the extent that the Federal Circuit may have concluded that all -- or that, excuse me -- that safety is the only issue before the FDA when it is considering an Investigational New Drug application, or that a drug innovator may not harbor additional purposes in an experiment beyond the FDA exemption, or that the -- excuse me -- beyond FDA regulatory purposes -- or, third, that the exemption does not cover efforts to optimize the drug candidate after it's identified and that candidate is, in fact, the lead candidate.

Those are the three legal theories, Your Honors, on which Integra is resting its defense of the judgement below. And every single one of them is either incorrect as a matter of law or immaterial as a matter of law. If

this Court were to ask Integra to come up with a single genuine issue of fact that does not relate to one or another of those three propositions, it will not be able to do so, save a footnote to be addressed later about the credibility of witnesses on a topic on which Integra never argued the witnesses were not credible.

Just beginning with the safety question, and I'll defer to the Government on that, because the Government can speak better than anyone else as to what it is that is relevant to the FDA in consideration of an IND, suffice it to say that the regulations say, as a matter of law, that safety is not the only consideration before the FDA as it considers an IND. The FDA cares very much about whether a drug will work: efficacy. The FDA cares very much about how it works: mechanism of action. It cares about what the body does to that drug: pharmacokinetics. And it cares very much about what that drug does to the body: pharmacology. And Integra's position before the jury, and before this Court, depends upon the proposition that it can bring in a witness to argue that the law is other than what the law clearly is. And the same thing goes for the so-called GLP studies that the FDA considers in connection with safety data, but need not limit itself to GLP studies when it's considering those other IND-relevant topics.

JUSTICE GINSBURG: Mr. Rosenkranz, just one piece of information. Because the IND is so important at this point, is it in the record -- do we have a copy of the IND?

MR. ROSENKRANZ: The IND, Your Honor, is not in the record, because it was excluded from evidence, which may be why the jury reached the wrong conclusion. But, I hasten to add, that will not be uncommon in these sorts of cases, because there are many circumstances in which a preclinical study begins and fails, and the IND will never materialize. There are circumstances in which a preliminary injunction is brought and won, and the research stops cold, so an IND never materializes.

And, again, it's important to understand, as one assesses the FDA exemption, that the inquiry is always ex ante, it is always, "What is a reasonable drug innovator? What does that drug innovator or scientist know at the point in time at which it is about to perform the next set of experiments?" So you always reflect back to a point in time before the IND materializes.

JUSTICE SCALIA: Mr. Rosenkrantz, the items you listed earlier seemed to me to more narrow than what I took to be the point of your opening brief, which was that the decision below was wrong because the Federal Circuit simply excluded all consideration of materials prepared

for purposes of the IND, as opposed to materials prepared for the -- for the drug application, later on. Are you abandoning that more expansive position?

MR. ROSENKRANZ: No, Your Honor.

JUSTICE SCALIA: Because I don't read the opinion that way. I don't think that opinion has to be read to say that they're not going to allow in anything that goes to the IND.

MR. ROSENKRANZ: Your Honor, there is certainly a way to read the Federal Circuit's opinion -- and this is also in response to Justice O'Connor's earlier question -- in which it did grapple with the very questions we're talking about now, and did answer the questions about whether it's just safety -- and I believe the Federal Circuit believed that only safety data were relevant; that is certainly what it indicated in oral argument -- and also that dual purposes are not permissible.

So let me now turn to the dual-purpose question, because it's another major theme of --

JUSTICE SCALIA: Have you answered my question? You're abandoning the assertion that the Federal Circuit did not consider anything that didn't go to the IND -- that didn't go to the --

MR. ROSENKRANZ: The --

JUSTICE SCALIA: -- drug application.

MR. ROSENKRANZ: No, Your Honor. I believe that there are two ways to read the Federal Circuit's opinion. To the extent that the Federal Circuit said nothing before the clinical stage is relevant to the FDA exemption -- if that is what the Federal Circuit held, we are -- we are not abandoning the position that that is wrong. I understand that there is another way to read the Federal Circuit's opinion that grapples with the subsidiary questions that we're discussing here, which are all fairly presented in our question presented. And that's what I'm addressing myself to now.

JUSTICE GINSBURG: So your first answer, are you relying what the Federal Circuit said in its opinion -- and it's in 10a of our cert petition appendix -- that is, the Federal Circuit's statement of the question presented, whether the preclinical research conducted under Scripps-Merck agreement is exempt from liability for infringement of Integra's patents.

MR. ROSENKRANZ: Yes, Your Honor. And then, two pages later, on 12a, the Federal Circuit states its conclusion, and I quote, "Thus, the Scripps work sponsored by Merck was not solely for use as reasonably related to clinical testing for the FDA."

JUSTICE SCALIA: Yeah, but it -- it's not at all clear in the opinion that the Court was using preclinical

and clinical in the very technical sense that you were -- that you use it, which means "clinical" is stuff submitted for the drug application, and "preclinical" is for the earlier application. That is not at all --

MR. ROSENKRANZ: Your Honor, it's not at all clear. And, just as in Boyle, when this Court faced a situation where it wasn't clear what the Federal -- or, excuse me -- what the Court of Appeals held, the Court --, "The best thing for this Court to do is to address what appears to be the threshold question that the Court of Appeals decided," but then also to address the subsidiary questions on the basis of which Integra is defending the judgement below.

JUSTICE SOUTER: Well, Mr. Rosenkranz --

CHIEF JUSTICE REHNQUIST: A moment ago -- a moment ago, you were reading from 12(a). Was it the first sentence you were reading from?

MR. ROSENKRANZ: I believe it was the first paragraph, and I was reading from the end of that paragraph, Your Honor, the -- which begins, "Thus," three lines -- really two -- the word "thus" is at the end of the third line from the bottom of that paragraph, Your Honor.

CHIEF JUSTICE REHNQUIST: Thank you.

MR. ROSENKRANZ: And so, I was saying earlier

that a critical component of Integra's case revolves around the notion that the use may not have more than one purpose, and that purpose can only be FDA directed. That argument is also incorrect as a matter of law. And one way we can tell that is that there is no such thing as a preclinical course of study that has only one purpose. When one is studying mechanism of action, a scientist is deeply interested, not just in how this drug works, but in how the disease works. And the language of the statute is, of course, the touchstone here. The statute is triggered by uses. The use, in this context, is an experiment. And the statute covers, provides a safe harbor for, experiments that develop the sorts of information that are relevant to the FDA. If that --

JUSTICE KENNEDY: Would that -- would that -- would that be explained by the research-tool doctrine, or not?

MR. ROSENKRANZ: No, absolutely not, Your Honor. The research-tool question -- let me begin by saying, these were not research tools; these RGD peptides were the objects of study.

JUSTICE KENNEDY: I guess what I was asking, Would you ever use the peptide as a research tool, was my -- was my question.

MR. ROSENKRANZ: Oh, yes, Your Honor. There are

circumstances in which these peptides could be used as research tools to stunt the growth of blood vessels and study what happens next with other compounds, but they were emphatically not used as research tools in this case. In this case, they were the objects of study, and Integra won a jury verdict based upon that presentation. In fact, never argued to any court or to the jury that there is a resource tool carve out. So, I was just talking about the subjective purpose earlier, and it is -- again, it's important to note that the information can be used for other purposes. There's nothing in the statute that prohibits that.

Now, let me turn, just briefly then, to what is often one of the most important questions in these FDA exemption cases, which is the timeline question. At what point in the arc of drug development is it unreasonable for a jury to conclude that the FDA is an inappropriate audience for the next set of experiments? Our position -- and people may differ, as a matter of law, as to whether it earlier -- but our argument is, at a bare minimum, at the point in time at which a drug developer has a known structure and cures a disease in an animal with that known structure, all eyes turn to drug development; which is to say, all eyes turn to the FDA. As a matter of law, everything after that, so long as it's relevant to the

FDA, is FDA -- is appropriate to view as FDA directed.

JUSTICE SOUTER: Do you agree then that at whatever period, however you want to describe the period, at which the researcher is basically trying to figure out what drug to concentrate on, that that period is too far back in time to come within the exception?

MR. ROSENKRANZ: No, Your Honor. That's exactly the trigger moment. If it has a structure, and it's investigating analogs of that structure to figure out which of these various structures are the best ones to move forward, everything from that point on is FDA directed.

JUSTICE SOUTER: Okay, here's what -- here's the problem I have with your argument. I can understand that argument more easily under the statute, under the text of the statute as it is written, than I can understand it under the instruction that you agreed to, because the instruction that you agreed to had a limitation, a textual limitation which is not in the statute itself, that refers to "relatively directly" as describing the relationship between this information and its object. And if we decide this case on the basis of the statute, and we read the statute more broadly than the instruction, then you're getting something that you're not entitled to, because you agreed to the instruction. If we decide this issue by

construing the statute as if your instruction is correct, then we're making an assumption about the proper construction of the statute that has not been argued here.

MR. ROSENKRANZ: Well, Your Honor --

JUSTICE SOUTER: It seems to me that the law of the case, as to what the statute means for your case, is set by the instruction, and that is why I am reluctant to get into the issue that you raise here, because I think we're rather -- you are limited, and we are tied in what we can do as a result of your agreement with the instruction.

MR. ROSENKRANZ: Your Honor -- and I see my time is running out; I'd like to reserve it for rebuttal, so let me, just briefly. Under Praprotnik, of course, this Court is not bound by law of the case by the instruction. But the instruction, as I understand it, says exactly what the statute says. "Reasonably directly" is simply another way of saying, "Are these activities reasonably related to the FDA purposes?" And every one of the comparative experiments is relevant to the FDA's inquiry, whether this drug or that is the optimum drug. Every experiment that is involved here -- and there were only 10 percent that were comparative in nature -- develops information about the lead drug candidate, including understanding why this one works, rather than that one.

So, if it's all right, Your Honors, I'd like to reserve the remainder of my time for rebuttal.

CHIEF JUSTICE REHNQUIST: Very well, Mr. Rosenkranz.

Mr. Joseffer.

ORAL ARGUMENT OF DARYL JOSEFFER

FOR UNITED STATES, AS AMICUS CURIAE,

SUPPORTING THE PETITIONER

MR. JOSEFFER: Mr. Chief Justice, and may it please the Court:

We believe the question before the Court is the proper construction of the statute, and we believe the lower courts committed three important legal errors that should be corrected.

The first is in drawing the clinical/preclinical distinction. And, understanding that, Justice Scalia, I think the important thing to understand is that clinical studies refer to studies conducted on humans, and at the IND stage, the whole question is to decide whether studies should be conducted on humans. So at that point in time the only information that's available is the preclinical studies on animals and in test tubes. So when the Court distinguished between preclinical and clinical, it was essentially saying, you cannot do the information that's necessary to submit an IND, necessary to do clinical

trials, necessary to get your drug approved. And that's why we -- it seems to us that that's clearly wrong.

CHIEF JUSTICE REHNQUIST: Do you have to have the FDA's permission to start clinical testing?

MR. JOSEFFER: Yes, that's the purpose of an IND application, is -- the whole -- the only thing that FDA is looking at, at that point, is whether to permit human clinical trials to proceed.

The second important legal error committed by the Federal Circuit was in apparently concluding that only tests regarding the compounds ultimately submitted to FDA in an IND are subject to the protection. Now, the problem with that is that a company can decide which specific compound to submit only by first comparing -- doing studies on that compound and on others in order to determine which would be the best compound to submit, which would strike the best balance between obtaining health effects or reporting safety concerns. So, if the exemption only --

JUSTICE O'CONNOR: Would you state again what you say the second error was?

MR. JOSEFFER: The second error, we believe, is that the Federal Circuit indicated that only studies undertaken on the single compound ultimately submitted in an IND are protected by the exception. And the problem

with that is that I can't figure out what that one compound is until I've done studies on it and on other compounds to determine --

JUSTICE SCALIA: That --

MR. JOSEFFER: -- which is the best to submit.

JUSTICE SCALIA: But that might well determine whether the research was relatively directly related. I mean, if I were a juror, I would -- I would say it's relatively directly related if it relates to that particular compound which is ultimately submitted, and not relatively directly related if it was preliminary, trying to found out which compound to submit.

MR. JOSEFFER: We would -- we would look at it this way. If I'm -- say I have 12 compounds that I'm going to test and decide which is best and go forward with. At the time I'm doing a test on any one of those compounds, if those tests succeed, it's reasonably foreseeable I'll submit an IND for that compound.

JUSTICE SCALIA: Yes, I understand all that. But --

MR. JOSEFFER: And the --

JUSTICE SCALIA: -- I'm just saying that that is certainly one interpretation of "reasonably directly." And if that is so, then you are erroneous in your assumption that the question before this Court is the

meaning of the statute. It might not be. It might be -- it might be the meaning of the instruction.

MR. JOSEFFER: Well, I think we would disagree with that, for two reasons. The first is that the Federal Circuit, as Justice O'Connor noted, reserved -- resolved these questions entirely as a matter of law, based on a de novo interpretation of the statute, without regard to the jury instruction. And that's the holding that's now before this Court.

JUSTICE O'CONNOR: What's your position on the jury instruction? Does it correctly state the law?

MR. JOSEFFER: We think that it's -- if it's construed correctly, we think that it's correct, but just too general to be of assistance to the courts in addressing the more specific questions of the issue here. And this is -- remember, Merck has sought judgement as a matter of law. And when a party seeks judgement as a matter of law, the courts are not constrained to only applying the law that's found in the jury instruction; they can also articulate and apply -- and do all the time -- other legal principles that are relevant. Praprotnik v. St. Louis is a great example of a case where this Court did that.

Now, there would be a problem if the jury instruction was inconsistent with the correct rule of law,

because then there could be a waiver concern. But we don't see that at issue here, because the jury instruction, we think, was just too general to speak to these issues.

But getting back to my point about why it can't be limited to that single compound --

CHIEF JUSTICE REHNQUIST: If in fact the jury instruction is too general. I mean, if both parties agreed to it, aren't they, in a sense, bound by it?

MR. JOSEFFER: We think that the Petitioner should not, and is not, arguing inconsistently with the jury instruction. The point is just that juries, being lay people, tend to be instructed --

CHIEF JUSTICE REHNQUIST: The Petitioner said he agreed with the core of the instruction, whatever that is.

MR. JOSEFFER: I think that's just with the general principles. Take, for example, a negligence case. Jurors are instructed all the time that the Defendant has a duty of ordinary care. And then courts, on appeal, will determine more specific legal questions, whether entire classes of conduct do or do not comply with the ordinary care, in much greater detailed instructions to the jury. And example of a case where this Court did that would be Shenker v. B&O Railroad, at 374 U.S. 1. And we think that in a -- in determining whether a Petitioner is entitled to

judgement as a matter of law, this Court should just articulate and apply the specific legal principles here; they're not inconsistent with the jury --

JUSTICE O'CONNOR: Was the court below wrong in saying that the statute was enacted only to help generic-drug development?

MR. JOSEFFER: Yes. In fact, this Court already held in Eli Lilly v. Medtronic that the statute is not limited to generic drugs. In fact, it's not even limited to drugs, but also applies to things like medical devices, food additives, color additives. And it's a very important point, because the Federal Circuit thought the statute to be construed in an artificially narrow manner in light of a supposed focus on generic drugs, which is just inconsistent with this Court's authoritative construction of --

JUSTICE SOUTER: Is that going to be your third point, the third error that the court supposedly committed?

MR. JOSEFFER: No, the third is the error committed by the District Court and relied on by Respondents here, which is the statement that FDA only considers safety, and not efficacy, in determining whether to permit human clinical trials to proceed. It's a very important point, because at the IND stage the question for

FDA is whether a drug should be given to human beings. And because there's no such thing as an absolutely safe drug, because all drugs entail at least some safety risks, FDA will not let human clinical trials proceed unless there's some reason to believe that the study could be useful. It's a -- it's a benefit-risk analysis. The Court looks to whether the potential benefits of the test would outweigh the risks of the test; and if not, the Court will not let a test proceed.

Now, Congress charged FDA with doing that by instructing FDA to determine whether the drug would pose an unreasonable risk to the health and safety of humans. And FDA has construed that, as I said, to mean the benefit-risk.

The most express articulation of that comes in the guidance document that FDA has put out regarding the preparation of the investigators brochure, which is a required part of the 9d submission. And the investigators -- and the guidance document explains that the investigators brochure must provide sufficient information for the -- for the reader to, quote, "make his/her own unbiased risk-benefit assessment of the proposed clinical." That's set forth on the bottom of page 10 of our brief. And --

CHIEF JUSTICE REHNQUIST: What are the

consequences if someone goes ahead and conducts a clinical trial without the approval of the FDA?

MR. JOSEFFER: That's contrary to federal law. I -- certainly would be severe civil consequences. And my guess is there are criminal consequences for doing that, too.

JUSTICE GINSBURG: Your time is short, so could you tell us how far back you think, under the statute, you can go and not -- and be within the safe harbor?

MR. JOSEFFER: Yes. We think that the proper test looks to whether a company is trying to develop a particular drug, by which we mean a substance with particular characteristics designed to achieve particular objectives. To explain that, we recognize that basic scientific research into human biology and disease processes is not protected. That's just too far down the stream of causation. But once I get a particular concept for a drug, this says I'm going to treat the disease in a particular way by targeting a particular part of the disease process. Then we think that the work done, going forward, with includes comparing different substances to figure out which would be the best active ingredient, is protected. To provide a concrete example --

JUSTICE SCALIA: Why isn't that basic research? I mean, I want to -- I want to treat this disease by

stifling the development of blood cells around it, or something like that, and then you ask yourself, "Gee, what would stifle the production of blood cells?" And let's assume there hasn't been any research done in that field before. You wouldn't consider that basic research, so long as the idea I have in my -- in my head is, I want to create a drug to treat this disease that will stifle blood cells?

MR. JOSEFFER: No. And here's why. The basic insight, and then I'll explain it, is that the first time a study -- a study is run on a particular substance, if that's -- first study is not protected, then the exemption is worthless, because I'd have to commit that infringing study before I came to the protection of the exemption.

So, we would say that the -- in this case, for example -- I think it's easier on particulars -- that basic research was figuring out that the key to cancer is -- the key to the growth of tumors is angiogenesis, and the key to blocking angiogenesis is blocking the alpha v beta 3 receptors. That's the basic research into how the body works. But once I then start trying to figure out which substance would best block an alpha v beta 3 receptor, it's very specific, because I know what that receptor is, I know what it's like, I know what characteristics I'm going to need in a drug to block that.

And when I try different things out to block that, that first experiment, at that point, has to be protected, because, otherwise, I'd have to commit the infringement before I could get --

JUSTICE KENNEDY: Did the earlier process that you described, the basic research, is that within the common law research exemption?

MR. JOSEFFER: The -- it would be if it was noncommercial.

JUSTICE KENNEDY: How does the common law of research exemption figure into this case, if at all?

MR. JOSEFFER: It's not directly you, Your Honor, because Petitioner has not relied on it at all, and for good reason, which is that the courts have consistently held that the common law research exception applies only to noncommercial activity. The most obvious example would be kids in their basements. But when a drug company, that its entire business is developing and manufacturing drugs, undertakes the activity, that's commercial, and that's never been considered protected by the common law exception.

JUSTICE KENNEDY: Does Scripps -- is Scripps in the business, too?

MR. JOSEFFER: I see my red light is on, if I could answer the question.

Some of Scripps' work, when it's working directly for Merck, certainly is, we would think, you know, tied closely to Merck's commercial activities. Scripps may also do some other --

CHIEF JUSTICE REHNQUIST: Thank you, Mr. Joseffer.

Mr. Flores.

ORAL ARGUMENT OF MAURICIO A. FLORES

ON BEHALF OF PETITIONER

MR. FLORES: Mr. Chief Justice, and may it please the Court:

This Court stated, in Black versus Cutter Laboratories, which is cited on page 27 of our brief, as follows, "At times, the atmosphere in which an opinion is written may become so surcharged that unnecessarily broad statements are made. In such a case, it is our duty to look beyond the broad sweep of the language and determine for ourselves precisely the ground on which the judgement rests."

This is such a case. The judgement of the Federal Circuit was its order affirming the District Court's denial of motion for judgement as a matter of law. The precise grounds for the Federal Circuit's opinion is set forth in page 14a in the appendix attached to Merck's petition for certiorari. And there the Federal Circuit

said that it upheld the denial of Merck's motion for judgement as a matter of law because the Federal Circuit discerned no error in the District Court's interpretation of section 271(e)(1), which raises the question --

JUSTICE GINSBURG: Where is this? Page 14a --

MR. FLORES: Yes, Your --

JUSTICE GINSBURG: What are you quoting from?

JUSTICE KENNEDY: Is it just before the letter "b" on 14a?

MR. FLORES: Yes, Your Honor.

JUSTICE BREYER: What are the first few words of the sentence there that you quoted?

MR. FLORES: "Because the language and context of the safe harbor do not embrace the Scripps-Merck general biomedical experimentation, this Court discerns no error" --

JUSTICE BREYER: Exactly. And so, they are saying that they're wrong on their ground for thinking that the language and context don't embrace it. Since they used the wrong standard, they never got to the question of whether the evidence warranted a directed verdict. So I don't see how we avoid looking at all of what you'd call the atmospherics.

MR. FLORES: The precise holding and the reasoning of the Federal Circuit was, they found no error

in what the District Court's --

JUSTICE BREYER: Because they interpreted the statute in a particular way. Isn't that right? I'm asking. I'm not --

MR. FLORES: No, Your Honor.

JUSTICE BREYER: No?

MR. FLORES: The only interpretation of the statute that can be found in the District Court's order denying Merck's motion for judgement as a matter of law is the standard articulated in the jury instruction.

JUSTICE SCALIA: No, but I think -- I think the Justice was asking whether it was the Court of Appeals that --

JUSTICE BREYER: Yes.

JUSTICE SCALIA: -- that applied a particular standard. And certainly it had to have been. Didn't the Court of Appeals have a particular standard as to what constituted general biomedical experimentation, as opposed to the kind of experimentation that's covered by the -- by the safe harbor exemption? It must have had. I mean, how could you -- how could you rule on the question before you unless you have, in your head, a notion of what the safe harbor consists of and what is beyond it?

MR. FLORES: The question before the Federal Circuit was whether the District Court erred by not

applying the rational predicate interpretation of section 271(e), which was the sole focus of Merck's appeal to the Federal Circuit.

JUSTICE GINSBURG: Why should we say that's the question, when the Federal Circuit, itself, said what I read before from 10a?

MR. FLORES: We're -- on page 10a, the Federal Circuit said, "Thus" -- and this is in the -- the last sentence in the middle paragraph of the page -- "Thus, this Court must determine whether section -- the section 271(e) safe harbor reaches back down the chain of experimentation to embrace development and identification of new drugs that will, in turn, be subject to FDA approval."

JUSTICE BREYER: That would answer that question?

MR. FLORES: It does not. The Federal Circuit answered that in the negative. The Federal Circuit rejected the interpretation advanced by Merck, which was the rational predicate standard, which was basically a causal test, and held that the District Court's interpretation, under the Intermedics standard that's given in the jury instruction, that Merck now concedes is the correct standard.

JUSTICE BREYER: So they say that does not -- the safe harbor does not reach, among other things, back

down the chain of experimentation to embrace the development of new drugs that will be subject to FDA approval. In your opinion, is that statement, as I read it -- I left out the word "identification" -- as I read it, is that statement a correct statement of the law, or incorrect statement?

MR. FLORES: That is a correct statement of the law.

JUSTICE BREYER: That is a correct statement of the law. So then, I take it, the other thinks that it isn't, because, for example, you could have a situation where you are developing drugs, and, in developing drugs, you do some experiments and you get some information that would be useful to the FDA and the IND process, and, therefore, they are within the safe harbor.

MR. FLORES: No, Your Honor. I believe the Solicitor General agrees with this aspect of the Federal Circuit's opinion and makes that clear at the bottom of page 15 and onto page 16 of the Solicitor General's brief. Merck no longer challenges this aspect of the Federal Circuit's opinion. Merck concedes that there are experiments in the basic research phase, that, although they're necessary in the chain of causation, are not exempt. The rational -- Merck has abandoned the rational predicate standard that the Federal Circuit rejected here.

JUSTICE GINSBURG: Mr. Flores, when I asked you about the sentence on page 10, I intended, not the one that you read, but an earlier one that precedes it, and that is, "The questioning arising in this case is whether the preclinical research" -- that is, the research on animals, as distinguished from humans -- "conducted under the Scripps-Merck agreement is exempt from liability for infringement of Integra's patents."

Now, if you just took that as the question, then you would say it -- this Circuit is drawing the line between clinical and preclinical. It's not a crystal-clear opinion, by any means, but that is one question presented that they've identified. And how do they answer that question?

MR. FLORES: Your Honor, I disagree. I think the operative language in this sentence is the reference to "the Scripps-Merck" -- is to "research conducted under the Scripps-Merck agreement."

JUSTICE SCALIA: That's the way I read it. It -- the -- and this is why I was disagreeing with counsel from the other side. It -- well, counsel ultimately conceded, you could read it not to draw the line between clinical and preclinical. And the way you read this sentence is -- the question, they say, is not whether preclinical research falls under 271(e)(1); it's whether

the "preclinical research conducted under the Scripps-Merck agreement." And then the next sentence explains what that means. The experiments did not supply information for submission to the United States Food and Drug Administration, but, instead, identified the best drug candidate.

So, I think what they're describing as the question presented is whether preclinical research that is -- that is not directed to supplying information for submission to the Food and Drug Administration, but, instead, to selecting the drug candidate, whether that type of preclinical research is within the safe harbor.

MR. FLORES: Yes. In fact, Justice Scalia, if this opinion by the Federal Circuit were interpreted to hold that preclinical experiments are categorically excluded from the scope of the exemption, that holding would be inconsistent with the District Court's interpretation of the law, because the District Court's interpretation of the law was that preclinical experiments are potentially eligible, and the District Court submitted the question to the jury.

So the Federal Circuit would be completely inconsistent, if, on the one hand, it categorically excluded preclinical experiments, and, on the other hand, it approved the District Court's --

JUSTICE BREYER: All right, this very dialogue makes me able to ask a question that I think will reveal better to you what I need an answer to.

Reading this, and listening to the discussion, and your use of the word "atmospherics," suggests that the opinion below is pretty foggy. We have Merck, the Food and Drug Administration, the Government, the entire biotechnology industry, the drug industry of the United States, and everybody else telling us that they are wrong in the way they stated the standard. And you, yourself, urge us to look beyond the way they stated it. So, what's the harm, and why wouldn't we, given this and the unclarity, just try to do a better job at stating the standard, say, "That's the standard," and then send it back, and then you can make all your arguments there about how it applies.

MR. FLORES: The reason it would not be appropriate for the Court to do so is because no standard, other than the Intermedics standard that was applied by the District Court, was ever suggested to the District Court. There was only one standard ever considered.

CHIEF JUSTICE REHNQUIST: We're not reviewing the District Court's opinion? We granted certiorari as to the particular question which will deal with what was the Court of Appeals opinion. We don't ordinarily simply

compare the Court of Appeals' opinion with the District Court's opinion to see if they parse.

MR. FLORES: Yes, Your Honor. But in this case the issue before the District Court was whether the District Court erred in denying a motion for judgement as a matter of law.

JUSTICE O'CONNOR: Well, don't you think that the Federal Circuit may have focused too much on generic drug applications? Do you think it was right about that?

MR. FLORES: I think the Federal Circuit was right, as a factual matter, describing the impetus for Congress adopting section 271(e).

JUSTICE O'CONNOR: Well, it seemed to be driven by its very narrow focus on generic drug development. Do you -- do you think that the efficacy of the drug being suggested plays a role in the IND application?

MR. FLORES: No, Your Honor, it does not.

JUSTICE O'CONNOR: See, I think there may be a difference there, because I think the other side thinks that how the drug is expected to work, in practice, and whether it, in fact, will attack a certain disease, is part of what the FDA looks at. Apparently, the Government takes that position, as narrowly as I could determine. But you reject that, as well.

MR. FLORES: Yes, Your Honor. I think the

answer to that is in the statute. It's a -- it's section -- it's 21 United States Code 355(i)(3)(B)(i). And in that --

JUSTICE O'CONNOR: Can you repeat that 355 what?

MR. FLORES: (i) --

JUSTICE O'CONNOR: -- (i) --

MR. FLORES: -- (3) --

JUSTICE O'CONNOR: Uh-huh.

MR. FLORES: -- (B)(i) again. And, in this section, Congress is telling the FDA what are the considerations that the FDA has to weigh in making the safety decision, the decision whether to allow clinical trials in humans --

JUSTICE GINSBURG: Is this text that you're referring to, is it someplace -- is the text someplace where we can look at it while you're explaining this to us?

MR. FLORES: No, Your Honor, it's not in the appendix, unfortunately. Let me read that statute, because it's instructive about what Congress told FDA to weigh for the --

JUSTICE O'CONNOR: But does the -- does the statute -- is that the only place we would look to decide whether safety is the only consideration for the FDA?

MR. FLORES: No, Your Honor. The regulations, I

believe, address that. And the regulations are 312.22(a), which is in the appendix attached to Integra's brief on the merits. And I'll read that. It says --

JUSTICE O'CONNOR: But you do --

JUSTICE SOUTER: What are you --

JUSTICE O'CONNOR: -- you do agree, do you not, that the Government does not agree with you on this point?

MR. FLORES: The Government disagrees, Your Honor.

JUSTICE O'CONNOR: Right.

JUSTICE SOUTER: What are you reading from?

MR. FLORES: Page 3a in the addendum to Integra's brief.

JUSTICE SOUTER: Okay.

MR. FLORES: That's 21 C.F.R. Section 312.22(a). It states that, "The FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in phase two and three, to help assure that the quality of the scientific investigation of the drugs is adequate to prevent an evaluation of the drug's effectiveness and safety."

JUSTICE SOUTER: Okay, that talks about the primary concern. There is certainly going to be concern with efficacy to this extent. They are going to want to know, before they allow clinical trials, whether the drug

that it is proposed to give cancer patients has some relationship to cancer, as opposed to the common cold. Admittedly, at the clinical trial they're trying to find out how effective it is on human beings, but there's got to be some threshold showing of effectiveness. They can't simply ignore effectiveness and look at safety entirely prior to that point.

JUSTICE STEVENS: In fact, that paragraph refers to effectiveness, as I read it.

MR. FLORES: Yes, it does, Your Honor. But it does -- it refers to it in the context of phases two and three. And the simple fact is that until there's clinical trials in humans, there's no way tell whether this drug a going to be effective.

JUSTICE SOUTER: But there is at least -- there's got to be some way to tell whether it even addresses the disease. That is essentially a threshold effectiveness question.

MR. FLORES: The FDA statutes and regulations do not use the term "efficacy" to describe that. In section 355(i)(3)(B)(i), when Congress listed the factors to consider, what it listed was not efficacy. Efficacy is not --

JUSTICE SOUTER: Congress described the need that there be some relationship between the consequences

of taking the given drug and the disease which is supposed to be addressed by taking the drug. If they didn't use the word "efficacy," what word did they use?

MR. FLORES: They --

JUSTICE STEVENS: They used the word "effectiveness," which is pretty close.

[Laughter.]

MR. FLORES: No, Your Honor, they used the word, in the statute, "the condition for which the drug is to be investigated."

JUSTICE BREYER: That's important. They say they want to know the pharmacological action of the drug in relation to its proposed therapeutic indication. The reason, I take it, the word "efficacy" is not there directly is because that word has a history, the Kefauver hearings, and it was involving drugs that don't do anything. Safety is a different matter. But of course when you consider whether something is safe, you must know, since, for example, cancer drugs poison people, the extent to which that poisoning is outbalanced by its effect in curing people. So how could you possibly, particularly where cancer is at issue, know whether this is an appropriately safe drug, without knowing how effective it is, as well as knowing the side effects that are -- that are harmful? If I knew that there was any

answer to that question at all, I might be tempted to agree with you, because it doesn't use the word. But what's the answer?

MR. FLORES: The answer is that the FDA considers what information is available to it. It does not have information about the effectiveness of the drug, because clinical trials have not taken place; and, therefore, the regulations and the statutes say you do the -- what you can. You look at the condition for which the drug --

JUSTICE GINSBURG: But why wouldn't it have information about effectiveness on animals? I mean, if the -- you show that the -- all the FDA's interested in is that it didn't kill the animal, never mind whether it was effective to cure the tumor?

MR. FLORES: The FDA is concerned with safety in animals. And there may be some cases in which there is a known safety risk to a drug, and there will be a heightened look at potential benefits in order to balance that out. But the regulations focus on safety. And in this particular --

JUSTICE O'CONNOR: Yeah, but it's absolutely clear, I thought, that the FDA, at the end of the day in some of these drug applications, ends up looking at not only safety, but how effective it is. And sometimes if

the safety risk is minimal but the effectiveness is great, I understood at least, that could affect the decisions. So, I would think that you would want to encourage the exemption to cover those matters.

MR. FLORES: Your Honor, of course FDA is very concerned about efficacy, and it -- but concerned about that after it gets data from human clinical trials. That's the -- that is the basis of --

JUSTICE O'CONNOR: No, I'm not sure. If there's data earlier, at IND stage, as a result of the lab tests and the animal tests, I would think that would be part of the exemption.

MR. FLORES: If efficacy -- or some information about what benefits the drug might have, is probably a better way to phrase it -- is considered at the safety stage as part of the safety balancing, then it's got to be done under good laboratory practices, because --

JUSTICE BREYER: Suppose that we concluded -- well, I don't want to cut you off. Go ahead, please. I cut you off.

MR. FLORES: If -- I believe the Solicitor General's point is that the safety decision is a practical one, and you've got to look at both sides of the ledger -- potential harm, potential benefit -- I don't believe it's proper to call that "efficacy." But whatever you call it,

if it's part of the safety balancing it has to be done under good laboratory procedures. That, I think, is clear from the FDA regulations. And, as a matter of policy, it wouldn't make any sense for the FDA to say that half of the safety equation need not be done under good laboratory practices. Both parts of the safety equation have to be done under that.

JUSTICE SCALIA: I don't -- so what? I don't understand what conclusion that leads to.

MR. FLORES: Well, Justice Scalia, let me say that I think that this whole discussion about the interpretation of the FDA law is really somewhat off the point here.

JUSTICE SCALIA: I was beginning to think that, too.

[Laughter.]

MR. FLORES: And the reason I say that is because we're not here to judge the legality of an FDA action in its discretion, saying we want to consider preclinical --

JUSTICE BREYER: Yeah, but the reason you brought it up is because the particular certificate that is for a safety-certified lab is not applicable to the lab that used this stuff. That's why you brought it up, I think.

MR. FLORES: That is correct.

JUSTICE BREYER: And I understand that. And you'd have to conclude, for them to win -- but suppose I did conclude -- suppose, for hypothetical -- the sake of -- for -- as a hypothetical, suppose I thought, yes, this does include the safety part, looking at how effective drugs are, too. Suppose I concluded that the statute meant sometimes you could do that, in an ordinary laboratory that didn't have the special certificate? Suppose I concluded that, indeed, you could look well in advance of the clinical test period to get the information for the IND? And suppose I concluded that sometimes, where it was reasonably related, you could, in fact, look at other drugs, too, that are related to the ones you do. If I concluded that -- and I'm not saying I would -- then would you concede that a directed verdict would have been appropriate against you?

MR. FLORES: No, Your Honor.

JUSTICE BREYER: Because? And what's your strongest argument that it wouldn't?

MR. FLORES: Well, Your Honor, there's numerous admissions in the record that Merck made which would indicate that they've -- that the program carried out at Scripps was not reasonably related to the FDA, that the real FDA work was being done in Germany, that the majority

of these experiments conducted by Scripps were conducted on chicken embryos, which Merck's own scientists agree have nothing to do with safety, and, by logical extension, they can't tell you much about efficacy, either. Merck agreed that a significant portion of these experiments in which Merck was looking for non-peptide compounds as possible drug candidates, is something that --

JUSTICE O'CONNOR: Well, we don't -- I hope we don't have to, at this Court, look at all the evidence and try to sort it out that way. What we have to focus on is whether the Court of Appeals for the Federal Circuit was in error in articulating the scope of the exemption.

MR. FLORES: Your Honor, this Court does not have to get into Rule 50 review of the evidence here --

JUSTICE O'CONNOR: No.

MR. FLORES: -- because there's no dispute about the legal standard. We've all heard that this morning. The only other possible issue is Rule 50 review. But Merck has failed --

JUSTICE O'CONNOR: Well, I thought the issue was whether the Court of Appeals for the Federal Circuit correctly determined the scope of the exemption. If they were wrong about it, then it is open to us to correct that and send it back.

MR. FLORES: Your Honor, the Federal Circuit

didn't determine the scope of the invention. There's -- it's --

JUSTICE O'CONNOR: Exemption. The statutory exemption. I thought that was what we were looking at.

MR. FLORES: Yes, that's what I was referring to. The Federal Circuit didn't articulate a standard for that. The Federal Circuit approved the District Court's use of the Intermedics standard, under which preclinical experiments are potentially --

JUSTICE O'CONNOR: Well, but it's certainly -- that the FDA considers only safety, and nothing else, that it was directed at generic drugs, not others, and that there was a cutoff point earlier than that argued by the Government and the Petitioner for what is exempt preclinical trial information.

MR. FLORES: The Federal Circuit's opinion, I believe -- the Federal Circuit's opinion rejects the rational predicate theory. It does not articulate an alternative standard to that. It merely ----

CHIEF JUSTICE REHNQUIST: They spent about ten pages in the appendix trying to do that.

MR. FLORES: But Federal Circuit didn't do that. That was discussion in there. It gave a lot of background about the statute, which may not have been necessary for its ultimate holding. But the Federal Circuit, when it

comes down to it, didn't do anything other than approve the District Court's interpretation.

Now, if the Federal Circuit did something different than that, which we just -- which is -- Integra does not believe is the case, its judgement should be upheld on the grounds articulated, that it could discern no error in the District Court's judgement -- in the District Court's denial of Merck's motion for judgement as a matter of law.

To respond to one of Justice O'Connor's earlier questions, "Does this Court have to get into a Rule 50 review," the answer is no, because Merck failed to preserve its right to Rule 50 review. In the District Court, in the Federal Circuit, the -- Merck argued the rational predicate standard as a matter of law. That was rejected.

Rule 50 review, under the Intermedics standard, is an entirely different argument, and Merck never raised that argument in -- before the Federal Circuit. In its brief, Merck relies, on pages 50 and 51 of its brief to the Federal Circuit, saying there it argued substantial evidence. But what it argued there was, the experiments are rational predicates. Merck never argued, before the Federal Circuit, that the verdict can't be sustained under Rule 50, under the Intermedics standard, as opposed to the

rational predicate standard, so it's not entitled to that review here.

JUSTICE GINSBURG: The dissenting judge did not -- the dissenting judge, Judge Newman, did not read the Court's opinion the way you do. Is that correct?

MR. FLORES: That is correct, Your Honor.

JUSTICE GINSBURG: Maybe we should take that into account, to some extent, that someone who participated on the bench had a different take on what her colleagues were saying?

MR. FLORES: That is certainly a consideration, but we disagree with Judge Newman on that point.

JUSTICE KENNEDY: Is there a difference between you and Merck concerning the scope and extent of the common law research exemption? And if there is, does that even enter into our case?

MR. FLORES: That issue hasn't entered into the case, so there's been no differences articulated, Your Honor.

And to get back to the point that Merck did not preserve its right to Rule 50 review under the Intermedics standard, even if it had raised that issue before the Federal Circuit, clearly the Federal Circuit didn't reach that issue. And if the Federal Circuit didn't reach an issue that was properly presented before it, that was

error, and Merck would have had to seek relief from that error. And it did not do so in its petition for certiorari. So, I do not believe this Court even needs to address the issue of Rule 50 review.

There is no dispute in this case as to the substantive standard that governs the scope of Section 271(e)(1), and Merck, having failed to preserve its rights to Rule 50 review under the Intermedics standard, there his no controversy for this Court to decide.

If the Court does reach the issue of Rule 50 review under Intermedics, it is -- the case should be decided under the basic principles that it is the exclusive province of the jury to weigh the evidence and to determine the credibility of the witnesses.

And my time is up, but -- almost -- but I'll say one thing. After 25 days of trial, the District Judge, in his denial of Merck's motion for judgement as a matter of law, expressly said that the jury had reasonable cause to disregard the testimony of Merck's main witness, Dr. Cheresh. And, on that ground alone, the judgement with the Federal Circuit should be sustained. Merck can't be rescued from the jury's verdict unless this Court determines, as a matter of law, that the jury was required to believe the testimony of Dr. Cheresh. And Merck can't show that, and hasn't even attempted to show that.

Unless there are any questions --

CHIEF JUSTICE REHNQUIST: Thank you, Mr. Flores.

Mr. Rosenkranz, you have two minutes remaining.

REBUTTAL ARGUMENT OF E. JOSHUA ROSENKRANZ

ON BEHALF OF PETITIONER

MR. ROSENKRANZ: Thank you, Your Honor.

With my two minutes, I want to make one overarching important point, and it's really in response to a question Justice Scalia asked.

The emphasis in the statute is about the use, so let's get past labels about, Is this drug discovery or basic research, or is it, as Merck says, optimization on the lead drug candidate, and look at exactly what was occurring here. Here, this was not a, "Gee, we'd like to see what affects angiogenesis." Merck knew what affected angiogenesis. It had a structure. And if you look at page 42 of the supplemental appendix, you will see that structure. It knew exactly what that structure did and how it did it. It then tweaked it by changing, literally, three atoms to compare that activity with other activity, exactly the sorts of research that any drug innovator would do to verify that they have the best and most effective candidate. Then, with -- and with every single one of its experiments, it was examining information that was relevant to mechanism of action, pharmacology,

pharmacokinetics, and efficacy. With 10 percent of the experiments, it was also running them in parallel with a series of analogs that were designed to look exactly like the RGD peptides, and to work exactly like the RGD peptides. And no rational drug innovator ever proceeds to clinical trials, nor does the FDA want it to, without conducting that research, because you don't spend millions of dollars for expensive toxicology studies until you know you've got the safest and most effective drug candidate. The FDA reviews that evidence, because it wants to know why you're proceeding with that candidate. And if you shift midstream to another lead, as Merck, in fact, did in this very case, the FDA wants to understand why.

So each of those experiments, even in comparison, developed information that is relevant to the FDA.

Thank you, Your Honors.

CHIEF JUSTICE REHNQUIST: Thank you, Mr. Rosenkrantz. The case is submitted.

[Whereupon, at 11:03 a.m., the case in the above-entitled matter was submitted.]